9. (ONCE AMENDED) The uricase of Claim 4, wherein the uricase has substantially the sequence as set forth in SEQ ID NO:2, wherein tyrosine 97 has been replaced by histidine.

10. (ONCE AMENDED) The uricase of Claim 4, wherein the uricase comprises an amino terminus and a carboxyl terminus, and wherein the uricase is truncated at one terminus or both termini.

REMARKS

Applicants have amended claims 8 and 9. The specific changes to the amended claims are shown on a separate set of pages attached hereto and entitled VERSION WITH MARKINGS TO SHOW CHANGES MADE, which follows the signature page of this Amendment. On this set of pages, the insertions are underlined, while the **[deletions are in brackets and bolded]**. Applicants respond below to rejections and objections raised by the Examiner in the Office Action of April 6, 2001.

I. Election/Restrictions

Applicants hereby elect, without traverse, to prosecute the group of claims identified as Invention I, *i.e.*, Claims 1-28 and 33 drawn to uricases. Applicants further elect to prosecute the species mammalian uricase. Applicants note that upon the allowance of a generic claim, Applicants will be entitled to consideration of claims to additional species, including fungal, microbial, invertebrate, and plant uricases.

II. Information Disclosure Statement

The Examiner has indicated that an English abstract to the Donadio *et al.* reference was not provided. Applicants regret any inconvenience that this may have caused. Applicants have attached herewith an English abstract for the reference for the Examiner's review.

III. Drawings

Applicants acknowledge the draftsperson's comments set forth on the PTO-948 attached to the Office Action. Applicants will provide formal drawings prior to the remittance of any issue fee.

IV. Objection to Claim 10

The Examiner alleges that Claim 10 does not further limit Claim 1, upon which it depends. The Examiner alleges that Claim 1 is directed toward full-length enzymes only, whereas Claim 10 encompasses fragments thereof. Applicants respectfully traverse. Claim 1 is directed towards purified urate oxidases. The specification clearly and unambiguously defines "urate oxidase" to comprise both full-length enzymes and their respective fragments. For example, on page 2, line 10, the present specification incorporates by reference the specification of the related and co-pending U.S. Patent Application Serial No. 09/370, 084, on whose page 9, lines 8-10, it reads: "The uricase of the invention, whatever the origin, may also be in a form that is truncated, either at the amino terminal, or at the carboxyl terminal, or at both." Therefore, the term "uricase" in Claim 1 refers to a uricase molecule that may be full-length or may be truncated. Claim 10 further limits the scope of Claim 1 by encompassing only the truncated molecules.

In view of the above, Applicants respectfully request the Examiner to reconsider and withdraw the objection.

V. Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 5, 8, 9, and 10 stand rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite.

Claims 5 and 9

The Examiner alleges that the word "substantially" is indefinite and renders the metes and bounds of the invention unclear. Applicants respectfully traverse. Having "substantially the sequence of," in the context of the present invention, means that any mutations in the sequence are insubstantial. "Insubstantial" mutation means that such mutation does not take the resulting

sequence outside of the metes and bounds of the specification, *i.e.*, having activity less than 75% of the wild-type protein. Thus, a sequence having substantially the sequence of one of the proteins identified in the specification is a protein that contains mutations and the activity of the mutated protein is not less than 75% of the activity of the wild-type protein.

Claims 8 and 9

The Examiner alleges that the recitation of "PKS" in Claim 8 and the recitation of the specific mutation in Claim 9 are unclear. Applicants have amended both Claims 8 and 9 by incorporating SEQ ID NOs of the sequences encompassed by the claims.

Claim 10

The Examiner alleges that the recitation of "comprises an amino terminal and a carboxy terminus" in Claim 10 is redundant and therefore unclear. Applicants respectfully traverse. The recitation of the termini affords proper antecedent basis for the latter half of the claim where "one terminus or both termini" is recited.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the 35 U.S.C. § 112 rejections.

VI. Rejections under 35 U.S.C. §§ 102 and 103

Wu *et al.*

Claims 1-5 and 33 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Wu *et al.* (*PNAS, USA* **1989**, *86*, 9412-9416). Applicants respectfully traverse.

Wu *et al.* describe purification of uricases by electroelution on an SDS/PAGE (sodium dodecyl sulfate/ polyacrylamide gel electrophoresis) gel. See page 9412, first paragraph of the MATERIALS AND METHODS section. It is known to those of skill in the art that such a method denatures the purified protein to the extent that the purified, monomeric protein retains very little, if any, of the catalytic activity of the natural protein.

Preferred embodiments of the present invention purify the protein by ion-exchange chromatography (Example 1) followed by size-exclusion chromatography (Example 2). The

purified proteins are then PEGylated. Following PEGylation, the proteins retain at least 75% of the catalytic activity of the wild-type protein. This indicates that the purified proteins of the invention, prior to PEGylation, retain a larger percentage of the catalytic activity of the wild-type protein.

Since the method of Wu *et al.* produces a protein that has little to no catalytic activity, whereas the methods of the present invention produce a protein that retains a substantial amount of the catalytic activity, Wu *et al.* do not anticipate the claims of the present invention.

Alvares *et al.*

Claims 1-2, 4, and 33 stand rejected under 35 U.S.C. § 102(b) for allegedly being unpatentable over Alvares *et al.* (*PNAS, USA* **1992**, *89*, 4909-4912). Applicants respectfully traverse.

Applicants respectfully submit that it is unclear which claims stand rejected. The first sentence of the rejection recites Claims 1-2, 4, and 33, whereas the last sentence concludes that the reference anticipates Claims 1-5 and 33. The status of Claims 3 and 5, therefore, remains uncertain. In the interest of being fully responsive, Applicants have assumed that Claims 3 and 5 also stand rejected. However, Applicants respectfully request a clarification.

Similar to the method of Wu *et al.* (above), the method of Alvares *et al.* requires purification using SDS/PAGE. See page 4909, last paragraph, and page 4912, 2nd paragraph. Thus, the method of Alvares *et al.* also results in a purified monomeric protein that is denatured and retains little to no catalytic activity. Since the purified tetrameric proteins of the present invention retain at least 75% of their catalytic activity, Alvares *et al.* does not anticipate the claims of the present invention.

The above references of Wu *et al.* and Alvarez *et al.* do not teach or describe all of the claimed elements of the present invention. Consequently, the references fail to anticipate the claimed invention. Furthermore, there is no suggestion or motivation in the references, either alone or in combination, or in the general knowledge in the art that other methods of purification in general, and the methods of purification set forth in the present application specifically, would

result in a protein that, following PEGylation, would retain at least 75% of the catalytic activity of the native protein. The Examiner has failed to establish a *prima facie* case of obviousness.

Caliceti *et al.*

Claims 1, 4, 17, 22, 25-17, and 33 stand rejected under 35 U.S.C. § 102(a) for allegedly being unpatentable over Caliceti *et al.* (*Bioconjugate Chem.* **1999**, *10*, 638-646). Applicants have attached herewith a declaration under 37 C.F.R. § 1.131 by Dr. L. David Williams, one of the inventors of the present invention, in which Dr. Williams sets forth the facts to establish that the subject matter of the present invention was invented prior to the publication date of Caliceti *et al.* Therefore, Caliceti *et al.* is not available as a prior art reference under 35 U.S.C. § 102(a).

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. §§ 102 and 103.

CONCLUSION

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the claims pursuant to statutory sections 112, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. In light of these amendments and remarks, reconsideration and withdrawal of the outstanding rejections is respectfully requested.

Any claim amendments that are not specifically discussed in the above remarks are not made for patentability purposes, and it is respectfully submitted that the claims satisfy the statutory requirements for patentability without the entry of such amendments. These amendments have been made only to increase claim readability, to improve grammar, or to reduce the time and effort required of those in the art to clearly understand the scope of the claim language.

If the Examiner has any questions that may be answered by telephone, he or she is invited to call the undersigned directly.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Oct. 4, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE.

8. (ONCE AMENDED) The uricase of Claim 7, wherein the chimeric uricase **[is PKS uricase]** has the sequence set forth in SEQ ID NO:3.

9. (ONCE AMENDED) The uricase of Claim 4, wherein the uricase has substantially the sequence **[of baboon liver uricase in which tyrosine 97 has been replaced by histidine]** as set forth in SEQ ID NO:2, wherein tyrosine 97 has been replaced by histidine.

10. (ONCE AMENDED) The uricase of Claim 4, wherein the uricase comprises an amino **[terminal]** terminus and a **[carboxy]** carboxyl terminus, and wherein the uricase is truncated at one terminus or both termini.

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